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Chiesi

2 SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: CHF 5259 pMDI	**Volume:**	
Name of Active Ingredient: Glycopyrrolate	**Page:**	

Title of Study:	Randomised, double-blind, placebo-controlled, cross-over study to investigate the bronchodilator efficacy and safety after single and repeated administrations of different doses of glycopyrrolate via pMDI in moderate to severe COPD patients
Investigator:	[redacted] MD
Study Centre(s):	[redacted] (United Kingdom)
Publication (Reference): None	
Studied Period: 2 August 2010 – 10 August 2011	**Phase of Development:** II

Objectives:

Primary Objectives

Part 1:

To assess the safety and tolerability of single administration of CHF 5259 via a pressurised Metered Dose Inhaler (pMDI) at 5 dose levels in subjects with moderate to severe chronic obstructive pulmonary disease (COPD)

Part 2:

To assess the bronchodilator efficacy of CHF 5259 pMDI at 3 dose levels by comparison with placebo in subjects with moderate to severe COPD after repeated administration

Secondary Objectives

Part 1:

To assess the bronchodilator efficacy of single administration of CHF 5259 pMDI at 5 dose levels by comparison with placebo in subjects with moderate to severe COPD.

Part 2:

- To evaluate the duration of bronchodilation
- To assess the safety and tolerability of repeated doses of CHF 5259 pMDI
- To evaluate the pharmacokinetic (PK) profile after single and repeated administration of CHF 5259 pMDI

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Methodology *(Study Design)*:

The study consisted of 2 parts:

Part 1 was conducted according to a single-centre, randomised, double-blind, placebo-controlled, single-dose escalation, alternating cross-over design in 2 cohorts of COPD subjects. Five CHF 5259 single-dose levels were assessed. The escalation scheme ensured a good control of the increase of the doses.

Subjects were divided into 2 cohorts:

- Cohort A was administered 3 dose levels (12.5 µg, 50 µg, and 200 µg) CHF 5259 pMDI and placebo according to a randomisation scheme that included 4 treatment sequences.
- Cohort B was administered 2 dose levels (25 µg and 100 µg) CHF 5259 pMDI and placebo according to a randomisation scheme that included 3 treatment sequences

Treatment sequences were defined as such to assure that in both cohorts during each treatment period 10 subjects received CHF 5259 pMDI and 2 subjects received placebo.

During each period, 1 of the 2 cohorts was dosed (i.e., the dose escalation was alternated between the 2 cohorts). Dose levels of CHF 5259 pMDI were escalated following completion of a cohort at a lower dose level if supported by an acceptable safety and tolerability profile. The time between consecutive treatment periods was about 7 days, but it could vary depending on the availability of the data and the time for evaluation and decision of the Study Safety Board. In any case, the wash-out period for each subject was to be no less than 7 days.

A follow-up visit was performed 7 to 14 days after the last administration of study drug.

Part 2 started after safety review of Part 1 and was conducted according to a randomised, double-blind, placebo-controlled, 4-period, 4-treatment, repeated-dose, cross-over design followed by an open-label extension period with tiotropium.

Part 2 comprised a total of five 8-day repeated-dose periods, separated by a 7-day (± 2 days) wash-out period. In the first 4 periods (core periods), the subjects were administered CHF 5259 pMDI (3 dose levels: 12.5 µg, 25 µg, and 50 µg twice a day [b.i.d.]) or placebo according to a cross-over design. The fifth period (extension period), was an 8-day open-label extension period with tiotropium (18 µg once a day [o.d.]).

On Day 8 of all treatment periods, subjects took a single dose of formoterol on top of CHF 5259 pMDI, placebo, or tiotropium in order to evaluate the additive effect on lung function over 12 h post-dosing.

A follow-up visit was performed 7 to 14 days after the last administration of study drug.

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Number of Subjects *(Planned and Analysed)*:

Part 1: at least 24 subjects were planned to be randomised (12 subjects per cohort).

At least 11 evaluable subjects per cohort were required during each treatment period for safety evaluation. In Cohort A, initially 12 subjects were randomised. Four subjects prematurely discontinued the study and were replaced in order to allow safety evaluation of at least 11 evaluable patients for each dose level. In Cohort B, 11 subjects were randomised. The safety population in Part 1 thus consisted of 27 subjects. The number of subjects in Part 1 per period and treatment is shown below:

Period	**Placebo, n**	**CHF 5259 pMDI, n**
Cohort A – Period 1 (12.5 µg)	2	10
Cohort B – Period 1 (25 µg)	2	9
Cohort A – Period 2 (50 µg)	2	10
Cohort B – Period 2 (100 µg)	2	9
Cohort A – Period 3 (200 µg)	2	10

N= number of subjects in the safety population

Part 2: approximately 40 subjects were planned to be randomised in order to obtain 32 evaluable subjects.

Thirty-eight subjects were randomised to one of 4 treatment sequences. The number of subjets in each of the defined populations is shown below:

Population, n	**Placebo**	**CHF 5259 pMDI**			**Tiotro-pium**
		25 µg	**50 µg**	**100 µg**	
Safety population	**35**	**36**	**34**	**38**	**34**
ITT population	**35**	**36**	**34**	**38**	**34**
PP population	**34**	**35**	**34**	**38**	**-**
Excluded due to poor compliance	0	1	0	0	-
Excluded due to forbidden medication	1	0	0	0	-
PK population	**-**	**36**	**34**	**38**	**-**

N= number of subjects in the population

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Diagnosis and Main Criteria for Inclusion:

1. Male and female subjects aged 40-75 years.
2. Diagnosis of moderate-severe COPD, according to the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines (2009).
3. Post-bronchodilator forced expiratory volume in 1 second (FEV_1) between 40% and 80% predicted values (40% ≤ FEV_1 ≤ 80%), documented at screening visit.
4. Post-bronchodilator FEV_1/forced vital capacity (FVC) ≤ 0.70 (absolute value) documented at screening visit.
5. Airway reversibility of at least 100 mL within 30 to 45 min after inhalation of ipratropium 80 µg (for Part 2: historical reversibility was acceptable for subjects who performed Part 1).

Test Product, Dose and Mode of Administration, Batch Number:

Glycopyrrolate bromide (CHF 5259), 12.5 or 25 µg per actuation, solution for inhalation:

Batch numbers for glycopyrrolate bromide in Part 1: [redacted] (12.5 µg) and [redacted] (25 µg);

Batch numbers for glycopyrrolate bromide in Part 2: [redacted] (12.5 µg) and [redacted] (25 µg).

Reference Therapy, Dose and Mode of Administration, Batch Number:

- Placebo, solution for inhalation, batch numbers: [redacted] (Part 1) and [redacted] (Part 2)
- Tiotropium (only in Part 2), 18 µg inhalation powder, hard capsule, batch number: [redacted]

Duration of Treatment:

Part 1: 3 single doses of CHF 5259 pMDI or placebo in Cohort A and 2 single doses of CHF 5259 pMDI or placebo in Cohort B, separated by a wash-out of at least 7 days.

Part 2: 4 8-day repeated dose treatment periods with CHF 5259 pMDI or placebo + 1 8-day treatment period with tiotropium o.d., separated by a wash-out of 7 ± 2 days. On Day 8 of each treatment period, all subjects took a single dose of formoterol on top of CHF 5259 pMDI, placebo, or tiotropium.

Criteria for Evaluation:

<u>Efficacy in Part 1</u>

- Trough FEV_1 at 12 h post-dose (defined as the mean of two measurements at 12 and 12.5 h post-dose)
- Trough FEV_1 at 24 h post-dose
- FEV_1 area under the measurement curve (AUC) from administration to 12 h post-dose ($AUC_{0\text{-}12h}$) corrected for time (computed using the linear trapezoidal rule)
- FEV_1 AUC from administration to 24 h post-dose ($AUC_{0\text{-}24h}$) corrected for time
- peak FEV_1
- FEV_1, FVC, and FEV_1/FVC

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Criteria for Evaluation, Cont'd:

- Trough FEV_1 at 12 and 24 h post-dose adjusted for baseline
- Peak FEV_1 adjusted for baseline
- FEV_1 $AUC_{0\text{-}12h}$ corrected for time adjusted for baseline
- FEV_1 $AUC_{0\text{-}24h}$ corrected for time adjusted for baseline

Efficacy in Part 2

Primary efficacy variable: trough FEV_1 at 12 h post-dose on Day 7 (before evening administration) (core periods)

Secondary efficacy variables:

- Core periods:
  - Trough FEV_1 at 12 h post-dose on Day 1 (before the evening administration)
  - Trough FEV_1 at 12 h post-dose on Day 8 (before the evening administration)
  - FEV_1 $AUC_{0\text{-}12h}$ corrected for time on Days 7 and 8
  - Trough FEV_1 at 12 h post-dose adjusted for baseline on Days 1, 7 and 8
  - FEV_1 $AUC_{0\text{-}12h}$ corrected for time and adjusted for baseline on Days 7 and 8
  - Pre-dose FEV_1 on Days 7 and 8 (post-hoc analysis)
- Extension period:
  - Trough FEV_1 at 24 h post-dose on Day 7 (before the morning administration on Day 8)
  - FEV_1 $AUC_{0\text{-}24h}$ corrected for time on Day 7
  - Trough FEV_1 at 24 h post-dose adjusted for baseline on Day 7
  - FEV_1 $AUC_{0\text{-}24h}$ corrected for time and adjusted for baseline on Day 7
- Core and extension periods:
  - Peak FEV_1 on Days 7 and 8
  - FEV_1, FVC, and FEV_1/FVC
  - Body plethysmography parameters on Day 7: specific airway conductance (sGaw), airway resistance (Raw), expiratory reserve volume (ERV), functional residual capacity (FRC), vital capacity (VC), inspiratory capacity (IC), and intra-thoracic gas volume (IGV), total lung capacity (TLC), residual volume (RV), and RV/TLC
  - $AUC_{0\text{-}12h}$ corrected for time of body plethysmography parameters on Day 7
  - Peak FEV_1 adjusted for baseline on Days 7 and 8

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Criteria for Evaluation, Cont'd:

Pharmacokinetics in Part 2

- Calculated from the individual drug concentration versus time profiles on Day 1: AUC from administration to 30 min post-dose ($AUC_{0\text{-}30min}$), AUC from administration up to the last measurable concentration ($AUC_{0\text{-}t}$), AUC from administration to 12 h post-dose ($AUC_{0\text{-}12h}$), AUC extrapolated to infinity ($AUC_{0\text{-}\infty}$,), value and time of the maximum plasma concentration (C_{max} and t_{max}, respectively), terminal (apparent elimination) half-life ($t_{½}$), apparent total body clearance(CL/F), and apparent volume of distribution (Vz/F)
- Calculated from the individual drug concentration versus time profiles on Day 7 at steady state: $AUC_{0\text{-}30min,ss}$, $AUC_{0\text{-}t,ss}$, $AUC_{0\text{-}12h,ss}$, $C_{max,ss}$, $t_{max,ss}$, $t_{½,ss}$, CL/F_{ss} and Vz/F_{ss}, value and time of the minimum plasma concentration ($C_{min,ss}$ and $t_{min,ss}$, respectively), average concentration at steady state ($C_{av,ss}$), accumulation ratio (R_{ac})
- Calculated on Day 1 and on Day 7 at steady state: amount of glycopyrrolate excreted in urine during each collection interval on Day 1 ($Ae_{0\text{-}4h}$, $Ae_{4\text{-}12h}$,$Ae_{0\text{-}4h,ss}$, $Ae_{4\text{-}12h,ss}$) and over the entire period of sample collection ($Ae_{0\text{-}12h}$, $Ae_{0\text{-}12h,ss}$), fraction excreted unchanged (fe%, fe_{ss}%), and renal clearance (CLr, CLr_{ss})

Safety in Part 1

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs), including occurrence of paradoxical bronchospasm
- Serious AEs (SAEs) and AEs leading to study withdrawal
- Vital signs: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP)
- 12-lead electrocardiogram (ECG) parameters: ventricular heart rate, PR, QRS, QT, corrected QT intervals (QTcB, QTcF)
- Abnormal findings on 12-lead ECG
- 24-h ECG Holter recordings
- Clinical chemistry and haematology, urinalysis
- $AUC_{0\text{-}24h}$ corrected for time of HR, QTcF, and QTcB on Day 1 (post-hoc analysis)

Safety in Part 2

- AEs and ADRs, including occurrence of paradoxical bronchospasm
- SAEs and AEs leading to study withdrawal
- Vital signs: HR, SBP, DBP
- 12-lead ECG parameters: ventricular heart rate, PR, QRS, QT, QTcB, QTcF
- Abnormal findings on 12-lead ECG
- 24-h ECG Holter recordings
- Clinical chemistry and haematology, urinalysis

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Criteria for Evaluation, Cont'd

- $AUC_{0\text{-}12h}$ corrected for time of HR, QTcF, and QTcB on Days 1 and 7 (post-hoc analysis)
- Change from screening to Day 7 in mean HR derived from 24-h Holter ECG recording (post-hoc analysis)

Statistical Methods:

Populations for Analysis

Part 1: Analysis of efficacy and safety variables was performed on the safety population, defined as all randomised subjects who received at least one administration of the study medication.

Part 2*:* The primary efficacy variable was analysed both in the intent-to-treat (ITT) and per-protocol (PP) population, while secondary efficacy variables were analysed in the ITT population only. The ITT population was defined as all randomised subjects who received at least one administration of the study medication and who had any available post-baseline efficacy evaluation for at least one treatment period. The PP population was defined as all subjects from the ITT population who did not have any major protocol deviation, excluding major protocol deviations related to procedure deviations.

Analysis of safety variables was performed in the safety population, defined as all randomised subjects who received at least one administration of the study medication.

PK variables were analysed in the PK population, defined as all subjects from the safety population excluding subjects without any valid PK measurement and with major protocol deviations concerning PK.

Efficacy Variables in Part 1

- Trough FEV_1 at 12 h post-dose (mean of two measurements at 12 h and 12.5 h post-dose) and at 24 h post-dose, FEV_1 $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}24h}$ corrected for time, and peak FEV_1 were summarised by treatment using descriptive statistics.
- FEV_1, FVC, and FEV_1/FVC were analysed within treatments: mean changes from pre-dose to each time point post-dose were summarised using descriptive statistics. Time profile plots were presented for the mean absolute value and the mean change.
- The parameters derived from FEV_1 adjusted for baseline were summarised by treatment using descriptive statistics.

Efficacy Variables in Part 2

Primary Efficacy Variable

Trough FEV_1 at 12 h post-dose on Day 7 (before evening administration) was analysed using an analysis of covariance (ANCOVA) model with treatment, period and subject as fixed effects and baseline FEV_1 (pre-dose FEV_1 on Day 1 of each treatment period) as a covariate. Data from the extension period were not used in the estimation of the model. Comparisons between each dose of CHF 5259 pMDI and placebo were based on the p-values obtained from the model, adjusted for multiplicity using Hommel's method.

Statistical Methods, Cont'd

At each dose level, superiority of CHF 5259 pMDI over placebo was demonstrated if the adjusted p-value indicated a significant difference and if the point estimate for the difference between CHF 5259 pMDI and placebo was >0 (i.e., superiority over placebo demonstrated if the one-sided p-value was <0.025). Also presented were the 95% CIs for all pairwise treatment differences obtained from the model (unadjusted for multiplicity).

Secondary Efficacy Variables

- Trough FEV_1 at 12 h post-dose on Day 1 (before evening administration) and on Day 8, FEV_1 $AUC_{0\text{-}12h}$ corrected for time on Days 7 and 8, and peak FEV_1 on Days 7 and 8 were analysed using the same model as for the primary efficacy variable, but without multiplicity correction. Data from the extension period were not used in the estimation of the model.
- FEV_1 and FVC were analysed within treatments: mean changes from baseline (pre-dose on Day 1 of each treatment period) and from the pre-dose value on the day of the measurement to each time point post-dose were calculated with their 95% confidence intervals (CIs) and paired t-tests were performed. Time profile plots were presented for the mean absolute value and the mean changes.
- Trough FEV_1 at 24 h post-dose on Day 7 (before morning administration on Day 8), FEV_1 $AUC_{0\text{-}24h}$ corrected for time on Day 7, and peak FEV_1 on Days 7 and 8 during extension period were summarised using descriptive statistics. No formal comparison involving tiotropium was done.
- As an exploratory analysis, trough FEV_1 at 12 h post-dose (before evening administration), FEV_1 $AUC_{0\text{-}12h}$ corrected for time and peak FEV_1 on Days 7 and 8 during the core periods were compared within treatment in order to assess the effect of formoterol. Mean changes from Day 7 to 8 were calculated with their 95% CIs and paired t-tests were performed.
- sGaw, Raw, ERV, FRC, VC, IC, IGV, TLC, RV, and RV/TLC on Day 7 were analysed within treatments: changes from the pre-dose value expressed as ratios between geometric means at each time point post-dose were calculated with their 95% CIs and paired t-tests were performed. Time profile plots were presented for the geometric mean of absolute values and the change from the pre-dose value expressed as ratio between geometric means.
- Log-transformed $AUC_{0\text{-}12h}$ of body plethysmography parameters on Day 7 were analysed using an ANCOVA model with treatment, period, and subject as fixed effects. Data from the extension period were not used in the estimation of the model. $AUC_{0\text{-}12h}$ of body plethysmography parameters during extension period was summarised using descriptive statistics.

Statistical Methods, Cont'd

- Changes on $AUC_{0\text{-}12h}$ corrected for time of body plethysmography parameters versus pre-dose on Day 7 were calculated on log-transformed values and paired t-tests were performed. The mean and 95% CI of this ratio was calculated and back-transformed.
- The parameters derived from FEV_1 adjusted for baseline were summarised by treatment using descriptive statistics.
- Pre-dose FEV_1 on Days 7 and 8 in Part 2 were analysed using the same model as for the primary efficacy variable. Data from the extension period (tiotropium) were not used in the estimation of the model.

Pharmacokinetics

- Dose proportionality in terms of $AUC_{0\text{-}t}$, $AUC_{0\text{-}t,ss}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}12h,ss}$, $AUC_{0\text{-}\infty}$, C_{max} and $C_{max,ss}$ was evaluated using the power model, including the log-transformed pharmacokinetic parameters as dependent variables, the log-transformed dose as a covariate, period and sequence as fixed effects, and patient nested within sequence as random effect. The slope for log-transformed dose was estimated with its 90% two-sided CI to examine dose proportionality.
- $AUC_{0\text{-}30min}$, $AUC_{0\text{-}30min,ss}$, $C_{min,ss}$, $C_{av,ss}$, t_{max}, $t_{max,ss}$, $t_{min,ss}$, $t_{½}$, $t_{½,ss}$, R_{ac}, CL/F, CL/F_{ss}, Vz/F, Vz/F_{ss}, $Ae_{0\text{-}4h}$, $Ae_{0\text{-}4h,ss}$, $Ae_{4\text{-}12h}$, $Ae_{4\text{-}12h,ss}$, $Ae_{0\text{-}12h}$, $Ae_{0\text{-}12h,ss}$, fe, fe_{ss}, CLr and CLr_{ss} were summarised using descriptive statistics.

Safety in Part 1

- The number and percentage of subjects experiencing AEs, ADRs, SAEs and AEs leading to study withdrawal was summarised by treatment. The occurrence of paradoxical bronchospasm was of special interest. AEs were also summarised by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, including specific tables by AE intensity and drug causality.
- Quantitative laboratory parameters (clinical chemistry and haematology) and their mean changes from pre-dose were summarised by treatment using descriptive statistics. Shift tables from pre-dose to post-dose, with regard to normal range, were presented for all relevant laboratory parameters. Urinalysis data were listed.
- At each time point post-dose, the absolute value and the mean change from pre-dose (pre-dose-adjusted value) were summarised by treatment using descriptive statistics for vital signs and 12-lead ECG parameters. Time profile plots, both individual and by treatment, were presented for pre-dose-adjusted values.
- For both QTcB and QTcF, the number and percentage of subjects with a
  - QTc interval >450 ms, >480 ms, and >500 ms
  - change from pre-dose in QTc interval >30 ms and >60 ms

  at each time point post-dose and at any time point post-dose were presented by treatment.

Statistical Methods, Cont'd

- Abnormal findings on 12-lead ECG were summarised by treatment using descriptive statistics;
- 24-h ECG Holter recordings were listed.
- As a post-hoc analysis, the $AUC_{0\text{-}24h}$ corrected for time of HR, QTcF, and QTcB was calculated for Day 1. These variables were summarised using descriptive statistics.

Safety in Part 2

- The number and percentage of subjects experiencing AEs, ADRs, SAEs and AEs leading to study withdrawal was summarised by treatment. The occurrence of paradoxical bronchospasm was of special interest. AEs were also summarised by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, including specific tables by AE intensity and drug causality.
- Mean changes from baseline (pre-dose on Day 1 in each treatment period) to end of treatment (12 h post-dose on Day 8) in quantitative laboratory parameters (clinical chemistry and haematology) were calculated with their 95% CIs by treatment. Shift tables from reference to end of treatment, with regard to normal range, were presented for all relevant laboratory parameters.
- For both QTcB and QTcF, the number and percentage of subjects with a
  - QTc interval >450 ms, >480 ms, and >500 ms;
  - change from baseline (pre-dose on Day 1) in QTc interval >30 ms and >60 ms

  at each post-dose time point and worst outcome at any post-dose time point were presented by treatment.
- Abnormal findings on 12-lead ECG were summarised by treatment using descriptive statistics.
- 24-h ECG Holter recordings were summarized by treatment group using descriptive statistics.
- At each post-dose time point the following statistics were calculated by treatment for vital signs and 12-lead ECG parameters:
  - mean absolute value with its 95% CI;
  - mean change from the pre-dose value at the day of measurement (pre-dose-adjusted value) with its 90% CI;
  - mean difference versus placebo in change from pre-dose (pre-dose- and placebo-adjusted value) with its 90% CI.

  Time profile plots, both individually and by treatment, were presented for pre-dose and placebo-adjusted values.

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Statistical Methods, Cont'd

- As a post-hoc analysis, change from screening to Day 7 in mean HR derived from 24-h Holter ECG recording was summarised using descriptive statistics and submitted to an ANOVA model including treatment, period, and subject as fixed effects. The adjusted mean differences between each dose of CHF 5259 pMDI and placebo were estimated from the model.
- As a post-hoc analysis, the $AUC_{0\text{-}12h}$ corrected for time of HR, QTcF, and QTcB was calculated for Days 1 and 7. These variables were summarised using descriptive statistics.

Summary – Conclusions Part 1

Efficacy Results in Part 1

After a single dose of CHF 5259 pMDI (any dose), large positive changes from baseline (i.e., pre-dose on Day 1 in each treatment period) in FEV_1 and FVC values were observed. The highest mean FEV_1 and FVC values were observed during the first 4 h after inhalation of CHF 5259 pMDI. With any dose of CHF 5259 pMDI, the mean changes from baseline in FEV_1 were statistically significant at each time point up to 6 h post-dose and at some time points (depending on the dose) thereafter. After placebo inhalation, FEV_1 and FVC values were similar to or lower than the reference values.

Baseline-corrected values of trough FEV_1 values at 12 and 24 h post-dose, peak FEV_1 values, and FEV_1 $AUC_{0\text{-}12h}$, and $AUC_{0\text{-}24h}$ values were all considerably higher after a single dose of CHF 5259 pMDI than after inhalation of placebo. Higher doses of CHF 5259 pMDI led, in general, to better results. Mean changes from baseline were statistically significant with any dose of CHF 5259 pMDI for peak FEV_1 and FEV_1 $AUC_{0\text{-}12h}$, with 50 to 200 µg CHF 5259 pMDI for trough FEV_1 value at 12 h post-dose, with 25, 100, and 200 µg CHF 5259 pMDI for trough FEV_1 value at 24 h post-dose, and with 25, 50, 100, and 200 µg CHF 5259 pMDI for FEV_1 $AUC_{0\text{-}24h}$.

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Summary – Conclusions Part 1, Cont'd

Safety Results in Part 1

Treatment-Emergent Adverse Events	Placebo N=10	CHF 5259 pMDI 12.5 µg N=10	25 µg N=9	50 µg N=10	100 µg N=9	200 µg N=10
Most frequently reported AEs (in ≥ 2 subjects during any treatment)						
Headache	3 (30.0)	3 (30.0)	1 (11.1)	3 (30.0)	0	3 (30.0)
Oropharyngeal pain	1 (10.0)	0	0	0	2 (22.2)	0
Constipation	2 (20.0)	0	0	0	0	0
n (%) with AE(s)	8 (80.0)	5 (50.0)	3 (33.3)	5 (50.0)	4 (44.4)	4 (40.0)
n (%) of deaths	0	0	0	0	0	0
n (%) with SAE(s)	1 (10.0)	0	0	0	0	0
n (%) with AE(s) leading to permanent discontinuation of the study	1 (10.0)	0	0	1 (10.0)	0	0
n (%) with severe AE(s)	0	0	0	0	0	0
n (%) with AE(s) considered to be treatment-related by the Investigator	1 (10.0)	0	0	1 (10.0)	0	1 (10.0)

N = number of subjects in the safety population

No deaths occurred during Part 1 of the study. One subject had a treatment emergent SAE (lung neoplasm malignant) following inhalation with placebo. Two subjects were withdrawn from the study due to AEs: atrial fibrillation following inhalation of placebo and ventricular extrasystoles following treatment with 50 µg CHF 5259 pMDI.

Five (50.0%), 3 (33.3%), 5 (50.0%), 4 (44.4%), and 4 (40.0%) subjects had at least one TEAE following inhalation of 12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg CHF 5259 pMDI, respectively, versus 8 (80%) subjects following placebo inhalation.

All AEs were mild or moderate in severity.

By preferred term, the most frequently reported TEAE was headache. There were no relevant differences in the incidences of TEAEs between the treatments.

Treatment-emergent AEs that were considered to be treatment-related by the Investigator were observed in 1 subject following placebo (constipation) and in 1 subject each after treatment with 50 µg and 200 µg CHF 5259 pMDI (dry mouth).

None of the laboratory abnormalities in Part 1 of the study were reported as AE.

None of the subjects had a QTcF value above 480 ms or a QTcF increase versus baseline >60 ms. QTcF values >450 ms were scarce (i.e., in 1 [10.0%] subject after inhalation of 12.5 µg CHF 5259 pMDI and none in the other treatment periods) as were QTcF increases versus baseline >30 ms (i.e., 1 [≤11.1%] subject after inhalation of 25 and 50 µg CHF 5259 pMDI and none in other treatment periods).

Name of Company: Chiesi Farmaceutici S.p.A.	Individual Study Table Referring to Part of the Dossier	*(for National Authority Use only)*
Name of Finished Product: CHF 5259 pMDI	Volume:	
Name of Active Ingredient: Glycopyrrolate	Page:	

Summary – Conclusion Part 1, Cont'd

Abnormalities in 24-h Holter ECG recording were considered clinically relevant by the Investigator and were reported as AE in 1 (11.1%) subject after treatment with 25 µg CHF 5259 pMDI, 1 (10.0%) subject after treatment with 50 µg CHF 5259 pMDI, and 1 (10.0%) subject after treatment with 200 µg CHF 5259 pMDI (ventricular extrasystoles in all 3 subjects), and 2 (20.0%) subjects after treatment with placebo (ventricular extrasystoles in 1 subject and atrial fibrillation in the other).

No vital sign-related AEs were reported.

Summary – Conclusions Part 2

Efficacy Results in Part 2

The primary efficacy variable was the trough FEV_1 at 12 h post-dose on Day 7 in the core periods (CHF 5259 pMDI and placebo). After 7 days of treatment with multiple doses of CHF 5259 pMDI, at 12 h post-dose, trough FEV_1 comparison between each dose of CHF 5259 pMDI and placebo indicated superiority of CHF 5259 pMDI (any dose) over placebo (one-sided p-values adjusted for multiplicity <0.001). In addition, this difference in trough FEV_1 at 12 h post-dose on Day 7 between CHF 5259 pMDI and placebo was found to be clinically significant (adjusted mean of the treatment difference versus placebo ≥0.120 L) in the 50 µg and 100 µg CHF 5259 pMDI treatment periods.

Parameter	Placebo N=35	CHF 5259 pMDI 25 µg N=36	CHF 5259 pMDI 50 µg N=34	CHF 5259 pMDI 100 µg N=38
Baseline FEV_1 (L) (Day 1 pre-dose), Mean (95% CI)	1.398 (1.235; 1.561)	1.417 (1.244; 1.590)	1.394 (1.233; 1.554)	1.393 (1.238; 1.548)
Baseline-corrected trough FEV_1 (L) at 12 h post-dose on Day 7, Mean (95% CI)	-0.056 (-0.087; -0.025)	0.073 (0.023; 0.122)	0.083 (0.032; 0.134)	0.108 (0.055; 0.161)
Treatment differences vs. placebo				
Adjusted mean (95% CI)[a] p-value[b]	- - -	0.115 (0.076; 0.155) <0.001	0.142 (0.102; 0.182) <0.001	0.136 (0.096; 0.176) <0.001
Treatment differences between CHF 5259 pMDI doses		**50 vs. 25 µg**	**100 vs. 25 µg**	**100 vs. 50 µg**
Adjusted mean (95% CI)[a] p-value[c]	- - -	0.026 (-0.013; 0.066) 0.187	0.020 (-0.018; 0.059) 0.299	-0.006 (-0.045; 0.033) 0.764

N = number of subjects in the ITT population. Data presented are from subjects with available data; therefore the number of subjects included in the analysis per variable may be lower than the one provided (see source tables).

[a] Not adjusted for multiplicity; [b] One-sided p-value adjusted for multiplicity using Hommel's method. Superiority over placebo was demonstrated if p-value <0.025; [c] Two-sided p-value not adjusted for multiplicity.

Note: Only core periods (CHF 5259 pMDI and placebo) were considered for the estimation of the model; no comparison with tiotropium was made.

Summary – Conclusions Part 2, Cont'd

Efficacy Results in Part 2, Cont'd

The superiority of multiple-dose administration of CHF 5259 pMDI (any dose) over placebo derived from the primary efficacy variable was supported by statistical between-group comparison of other lung function derived parameters on Days 1, 7, and 8 (i.e., trough FEV_1 at 12 h post-dose on Day 1, peak FEV_1, FEV_1 $AUC_{0\text{-}12h}$ corrected for time, and pre dose FEV_1 on Day 7, peak FEV_1, FEV_1 $AUC_{0\text{-}12h}$ corrected for time, pre-dose FEV_1, and trough FEV_1 12 h post dose on Day 8), as well as of body plethysmographic parameter AUCs on Day 7 (sGaw $AUC_{0\text{-}12h}$, RV $AUC_{0\text{-}12h}$, and VC $AUC_{0\text{-}12h}$). All corresponding p-values were ≤0.002.

Between-dose comparisons also indicated statistically significant differences between CHF 5259 pMDI doses, in favour of the higher doses: i.e., 50 µg CHF 5259 pMDI was proved to be statistically significantly better than the 25 µg dose based on peak FEV_1 on Days 7 and 8, pre-dose FEV_1 on Days 7 and 8, FEV_1 $AUC_{0\text{-}12h}$ on Day 8, sGaw $AUC_{0\text{-}12h}$, and VC $AUC_{0\text{-}12h}$ on Day 7 (p-values ≤0.037). Statistically significant differences favouring 100 µg over 25 µg CHF 5259 pMDI were observed for the same variables, except for peak FEV_1 on Days 7 and 8 and VC $AUC_{0\text{-}12h}$ on Day 7. No statistically significant differences were established between the 50 and 100 µg CHF 5259 pMDI doses with respect to the derived lung function and body plethysmographic parameters.

In all 4 core periods of the study (i.e., CHF 5259 pMDI and placebo administration), mean trough FEV_1 at 12 h post dose, peak FEV_1, and FEV_1 $AUC_{0\text{-}12h}$ were statistically significantly better on Day 8 - when formoterol was administered on top of the study medication - than on Day 7 (p-values <0.001).

Pharmacokinetic Results in Part 2

The pharmacokinetics of glycopyrrolate was studied in plasma and urine up to 12 h after a single (Day 1) and a repeated (Day 7) administration of CHF 5259 pMDI. The study drug was administrated in a b.i.d. regimen with a total daily dose amounting to 25 µg, 50 µg or 100 µg.

Pre-dose plasma concentrations were always below the lower limit of quantification (BLOQ), except for Subject [redacted] in Treatment MD1 (the concentration was higher than 5% of the corresponding C_{max}; this subject was excluded from all assessments regarding this treatment).

Steady-state plasma concentrations were reached within 6 days of treatment, as indicated by pre-dose levels that were similar on Day 6 and Day 7.

The main pharmacokinetic parameters and the statistical analysis are shown in the following tables.

Name of Company: Chiesi Farmaceutici S.p.A.	Individual Study Table Referring to Part of the Dossier	*(for National Authority Use only)*
Name of Finished Product: CHF 5259 pMDI	**Volume:**	
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Summary – Conclusions Part 2, Cont'd

Pharmacokinetic parameter	CHF 5259 pMDI (Day 1 – single dose)		
	25 µg N=29	**50 µg N=32**	**100 µg N=37**
C_{max} (pg/mL)	24.3 ± 13.3	45.3 ± 26.6	86.3 ± 68.7
t_{max} (h)	0.08 (0.08-0.25)	0.08 (0.08-0.53)	0.12 (0.08-1.00)
$AUC_{0-30min}$ (pg.h/mL)	9.93 ± 4.41 [a]	17.7 ± 8.84 [d]	34.0 ± 24.0 [g]
AUC_{0-12h} (pg.h/mL)	38.4 ± 27.6 [a]	83.2 ± 54.1 [d]	180 ± 120 [g]
AUC_{0-t} (pg.h/mL)	32.3 ± 27.9 [a]	76.6 ± 55.4 [d]	177 ± 123 [g]
$AUC_{0-\infty}$ (pg.h/mL)	NC [b]	146 ± 55.4 [e]	273 ± 118 [h]
$t_{1/2}$ (h)	1.78 ± 1.48 [c]	2.52 ± 1.90 [f]	3.87 ± 2.53 [i]
CL/F (mL/min)	NC [b]	3180 ± 990 [e]	3858 ± 2278 [h]
V_z/F (L)	NC [b]	669 ± 220 [e]	1104 ± 306 [h]

N = number of subjects, NC = Not Calculated
Values are arithmetic means ± SD, except median (range) for t_{max}
[a] N = 25, [b] N = 1, [c] N = 23, [d] N = 30, [e] N = 10, [f] N = 28, [g] N = 35, [h] N = 16, [i] N = 32
The dose reported is the total daily dose. Pharmacokinetic profiles have been evaluated after the morning administration of half of the total daily dose (frequency was b.i.d.).

Pharmacokinetic parameter	CHF 5259 pMDI (Day 7 – repeated administration)		
	25 µg N=35	**50 µg N=33**	**100 µg N=35**
$C_{max,ss}$ (pg/mL)	39.4 ± 17.0 [a]	86.6 ± 46.2	160 ± 75.6
$t_{max,ss}$ (h)	0.08 (0.08-0.55) [a]	0.12 (0.07-1.00)	0.17 (0.08-0.52)
$C_{min,ss}$ (pg/mL)	BLOQ [*]	8.68 ± 4.61	17.3 ± 6.99
$t_{min,ss}$ (h)	0.00 (0.00-12.00)	8.05 (0.00-12.00)	12.00 (0.00-12.00)
$AUC_{0-30min,ss}$ (pg.h/mL)	14.6 ± 5.59 [a]	32.5 ± 15.5	60.7 ± 25.1
$AUC_{0-12h,ss}$ (pg.h/mL)	87.0 ± 41.7 [b]	223 ± 85.7 [b]	427 ± 152
$AUC_{0-t,ss}$ (pg.h/mL)	83.6 ± 42.7 [a]	218 ± 88.8	427 ± 153
$C_{av,ss}$ (pg/mL)	7.25 ± 3.47 [b]	18.6 ± 7.14 [b]	35.5 ± 12.7
$t_{1/2,ss}$ (h)	4.90 ± 3.13 [c]	11.8 ± 12.0 [e]	10.1 ± 7.09 [f]
CL/F_{ss} (mL/min)	3179 ± 2019 [b]	2283 ± 1276 [b]	2190 ± 743
V_z/F_{ss} (L)	1019 ± 536 [c]	1989 ± 1695 [e]	1998 ± 1537 [f]
R_{ac}	2.68 ± 1.68 [d]	4.27 ± 5.47 [c]	7.26 ± 13.7 [g]

N = number of subjects, NC = Not Calculated
Values are arithmetic means ± SD, except median (range) for t_{max} and t_{min}
Rac was calculated as $AUC_{0-12h,ss}$ (Day 7) / AUC_{0-12h} (Day 1)
[a] N = 34, [b] N = 32, [c] N = 28, [d] N = 24, [e] N = 26, [f] N =27, [g] N = 33
[*] SD not calculated because more than half of the individual values were BLOQ
The dose reported is the total daily dose. Pharmacokinetic profiles were evaluated after the morning administration of half of the total daily dose (frequency was b.i.d.).

Summary – Conclusions Part 2, Cont'd

Dose proportionality after a single administration of CHF 5259 pMDI

Glycopyrrolate C_{max} increased on average slightly less than dose proportionally throughout the dose range, as indicated by the slope (90% CI) of 0.752 (0.53-0.97). The systemic exposure measured by AUC_{0-t} and AUC_{0-12h} increased proportionally with the dose throughout the dose range, as indicated by the respective slopes (90% CI) of 1.06 (0.77-1.36) and 0.958 (0.69-1.23). The $AUC_{0-\infty}$ increased proportionally with the dose between the treatments 50 µg and 100 µg CHF 5259 pMDI, as indicated by the slope (90% CI) of 0.994 (0.66-1.33).

Dose proportionality after repeated administration of CHF 5259 pMDI

Glycopyrrolate $C_{max,ss}$ increased on average proportionally with the dose, as indicated by the slope (90% CI) of 1.02 (0.96-1.09).

The systemic exposure at steady-state measured by $AUC_{0-t,ss}$ and $AUC_{0-12h,ss}$ increased slightly more than dose proportionally throughout the assessed dose range, as indicated by the respective slopes (90% CI) of 1.25 (1.17-1.33) and 1.18 (1.11-1.25).

Pharmacokinetic parameter	CHF 5259 pMDI (Day 1 – single dose) PE (90%CI)[a]	Pharmacokinetic parameter	CHF 5259 pMDI (Day 7 – repeated administration) PE (90%CI)[a]
C_{max}	0.752 (0.53; 0.97)	$C_{max,ss}$	1.02 (0.96; 1.09)
AUC_{0-t}	1.06 (0.77; 1.36)	$AUC_{0-t,ss}$	1.25 (1.17; 1.33)
AUC_{0-12h}	0.958 (0.69; 1.23)	$AUC_{0-12h,ss}$	1.18 (1.11; 1.25)
$AUC_{0-\infty}$	0.994 (0.66; 1.33)		

PE = point estimate

[a] Point estimate and 90%CI of the slope of log-transformed dose from the power model.

The dose proportionality of $AUC_{0-\infty}$ was assessed between the treatments 50 µg and 100 µg CHF 5259 pMDI (n equalled 1 for $AUC_{0-\infty}$ in the 25 µg CHF 5259 pMDI treatment).

The average accumulation ratio (R_{ac}) at steady-state increased throughout the dose range, corresponding to 2.68, 4.27, and 7.26, in the treatments 25, 50, and 100 µg CHF 5259 pMDI, respectively. However, no differences between doses were observed, by comparing median values to minimize the impact of extreme values on R_{ac} (median [range] R_{ac} 2.19 [1.09-8.27], 2.52 [1.16-29.5], and 2.46 [0.99-71.1] in the 25, 50, and 100 µg treatments, respectively). The average minimum concentration at the steady-state ($C_{min,ss}$) increased with the dose, remaining BLOQ (5.00 pg/mL) in the 25 µg CHF 5259 pMDI treatment and corresponding to 8.68 pg/mL and 17.3 pg/mL in the 50 and 100 µg CHF 5259 pMDI treatments, respectively.

The excretion of glycopyrrolate in urine was studied up to 12 h post-dose on Day 1 (single-dose) and on Day 7 (repeated administration). The summary of glycopyrrolate urinary excretion pharmacokinetic parameters is presented in the following tables.

Name of Company: Chiesi Farmaceutici S.p.A.	Individual Study Table Referring to Part of the Dossier	*(for National Authority Use only)*
Name of Finished Product: CHF 5259 pMDI	Volume:	
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Summary – Conclusions Part 2, Cont'd

Pharmacokinetic parameter	CHF 5259 pMDI (Day 1 – single dose)		
	25 µg N=20	50 µg N=19	100 µg N=28
Ae_{0-12h} (µg)	0.671 ± 0.411	1.58 ± 0.823	2.69 ± 1.66
Ae_{0-4h} (µg)	0.417 ± 0.292	1.09 ± 0.507	1.73 ± 1.22
Ae_{4-12h} (µg)	0.255 ± 0.194	0.494 ± 0.378	0.956 ± 0.583
fe (% dose)	5.37 ± 3.29	6.32 ± 3.29	5.38 ± 3.32
CLr (mL/min)	396 ± 217 [a]	375 ± 171 [b]	287 ± 153 [c]

N = number of subjects
Values are arithmetic means ± SD
[a] N = 17, [b] N = 18, [c] N = 27
The dose reported is the total daily dose. Pharmacokinetic profiles were evaluated after the morning administration of half of the total daily dose (frequency was b.i.d.).

Pharmacokinetic parameter	CHF 5259 pMDI (Day 7 – repeated administration)		
	25 µg N=35	50 µg N=34	100 µg N=36
$Ae_{0-12h,ss}$ (µg)	1.62 ± 0.638 [a]	3.62 ± 1.80	6.94 ± 2.88
$Ae_{0-4h,ss}$ (µg)	0.861 ± 0.416	2.15 ± 1.30	4.18 ± 1.79
$Ae_{4-12h,ss}$ (µg)	0.750 ± 0.352 [a]	1.47 ± 0.679	2.76 ± 1.31
fe_{ss} (% dose)	12.9 ± 5.10 [a]	14.5 ± 7.19	13.9 ± 5.76
CLr_{ss} (mL/min)	356 ± 148 [b]	291 ± 95.5 [c]	281 ± 79.9 [d]

N = number of subjects
Values are arithmetic means ± SD
[a] N = 34, [b] N = 31, [c] N = 32, [d] N = 35
The dose reported is the total daily dose. Pharmacokinetic profiles were evaluated after the morning administration of half of the total daily dose (frequency was b.i.d.).

Both on Days 1 and 7 (single and repeated administration, respectively), average urinary glycopyrrolate excretion over 12 h post-dose increased proportionally with the dose. On each assessment day, the fraction excreted of unchanged glycopyrrolate was similar between all treatments (mean fe was 5.37 %, 6.32 %, and 5.38 % in the 25 µg, 50 µg, and 100 µg CHF 5259 pMDI treatments, respectively; fe_{ss} was 12.9 %, 14.5 %, and 13.9 %, respectively). More than 50% of the amount excreted was found in the 0-4 h post-dosing interval (ranging from 62 to 69 % on Day 1 and from 53 to 60 % on Day 7). The mean (± SD) renal clearance of glycopyrrolate slightly decreased throughout the dose range. CLr (Day 1) corresponded to 396 ± 217 mL/min, 375 ± 171 mL/min, and 287 ± 153 mL/min in the 25 µg, 50 µg, and 100 µg CHF 5259 pMDI treatments, respectively. The mean (± SD) CLr_{ss} (Day 7) corresponded to 356 ± 148 mL/min, 291 ± 95.5 mL/min, and 281 ± 79.9 mL/min, respectively. In all treatments, the amount excreted and fraction excreted of unchanged glycopyrrolate was increased after repeated administration compared to what was observed after the first dosing.

Name of Company: Chiesi Farmaceutici S.p.A.	Individual Study Table Referring to Part of the Dossier	*(for National Authority Use only)*
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Summary – Conclusions Part 2, Cont'd

Safety Results in Part 2

Treatment-Emergent Adverse Events	Placebo N=35	CHF 5259 pMDI 25 µg N=36	CHF 5259 pMDI 50 µg N=34	CHF 5259 pMDI 100 µg N=38	Tiotropium N=34
Most frequently reported AEs (in >2 subjects during any treatment)					
Back pain	2 (5.7)	1 (2.8)	1 (2.9)	1 (2.6)	3 (8.8)
Headache	6 (17.1)	4 (11.1)	7 (20.6)	4 (10.5)	4 (11.8)
Cough	4 (11.4)	1 (2.8)	1 (2.9)	0	0
n (%) with AE(s)	15 (42.9)	16 (44.4)	12 (35.3)	15 (39.5)	12 (35.3)
n (%) of deaths	0	0	0	0	0
n (%) with SAE(s)	0	0	0	0	0
n (%) with AE(s) leading to permanent discontinuation of the study	0	0	0	0	0
n (%) with severe AE(s)	0	0	0	0	0
n (%) with AE(s) considered to be treatment-related by the Investigator	1 (2.9)	2 (5.6)	0	1 (2.6)	2 (5.9)

N = number of subjects in the safety population

No deaths or any other SAEs occurred during Part 2 of the study. None of the subjects were withdrawn from the study due to AEs.

Sixteen (44.4%), 12 (35.3%), and 15 (39.5%) subjects had at least one TEAE during treatment with 25, 50, and 100 µg CHF 5259 pMDI, respectively. Fifteen (42.9%) subjects had at least one TEAE during placebo inhalation and 12 (35.3%) subjects had at least one TEAE during treatment with tiotropium.

All AEs were mild or moderate in severity.

By preferred term, the most frequently reported TEAEs during treatment with CHF 5259 pMDI (any dose) was headache.

Treatment-emergent AEs that were considered to be treatment-related by the Investigator were observed in 1 (2.9%) subject during placebo (2 events: cough and dry throat), in 2 (5.6%) subjects during 25 µg CHF 5259 pMDI (dry mouth and dysphonia in 1 subject each), in 1 (2.6%) subject during 100 µg CHF 5259 pMDI (2 events: dry throat and dysphonia), and in 2 (5.9%) subjects during tiotropium (dyspepsia and headache in 1 subject each).

Laboratory abnormalities were reported as AE for 1 subject (haemoglobin decreased on Day 8 of 100 µg CHF 5259 pMDI treatment.

Mean QTcF and HR increased from baseline to maxima at 3 or 12 h post-dose on Days 1, 7, and 8. Mean changes over time were however similar following all treatments and no correlation between glycopyrrolate plasma concentration and changes in QTcF or HR was observed.

Name of Company: Chiesi Farmaceutici S.p.A.	Individual Study Table Referring to Part of the Dossier	*(for National Authority Use only)*
Name of Finished Product: CHF 5259 pMDI	**Volume:**	
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Summary – Conclusions Part 2, Cont'd

None of the subjects had QTcF above 480 ms. Treatment-emergent QTcB value above 480 ms was seen in 1 (2.9%) subject, during treatment with tiotropium. QTcF values >450 ms were scarce, i.e., observed in 2 (5.9%) subjects each during 50 µg glycoppyrolate pMDI and tiotropium treatment and in 1 (≤2.9%) subject during the other treatments, placebo, 25 µg, and 100 µg CHF 5259 pMDI. Change in QTcF versus baseline >60 ms was observed in 1 (2.6%) subject during treatment with 100 µg CHF 5259 pMDI. Changes in QTcF >30 ms versus baseline were observed in at most 9 (23.7%) subjects during treatment with CHF 5259 pMDI (any dose), 4 (11.4%) subjects during placebo, and 7 (20.6%) subjects during tiotropium.

No 12-lead ECG-, 24-h Holter ECG-, or vital sign-related AEs were reported.

Conclusion:

Part 1

Single doses of CHF 5259 pMDI were safe and well tolerated, even up to 200 µg, in subjects with moderate to severe COPD.

Part 2

CHF 5259 pMDI was seen to be superior to placebo in terms of the primary efficacy variable, trough FEV_1 at 12 h post-dose on Day 7, and for all secondary efficacy variables based on FEV_1 evaluated on Days 1, 7, and 8 of multiple dose administration. This was true for all doses of CHF 5259 pMDI tested (25, 50, and 100 µg).

Multiple dose administration of CHF 5259 pMDI up to 100 µg for 8 days was safe and well tolerated in subjects with moderate to severe COPD.

Date of report: 19-July-2012 [redacted]